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Central interaction of ascorbic acid and D2 dopamine receptors on spatial learning and memory in adult male rats

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Abstract

Previous studies had reported that extracellular levels of ascorbic acid have modulatory effects on dopamine receptors. Both ascorbic acid and dopamine receptor have an important role in learning and memory processes. However, the central interaction between ascorbic acid and dopamine D2 receptor on spatial learning and memory has not yet been elucidated.

All experiments were carried out on male Wistar rats. Animals were subjected to 5 days of training in the Morris water maze (MWM) task; 4 days with an invisible platform to test special learning and the 5th day with a visible platform to test motivation and sensorimotor coordination.

The data showed that ascorbic acid (25 µg, i.c.v.) could improve spatial learning and memory indices. Administration of bromocriptine, a D2 agonist, increased the effect of ascorbic acid, while treatment with the selective D2 antagonist sulpiride resulted in prevention of the ascorbate-induced memory consolidation. These results indicate that dopamine D2 receptors may be involved in ascorbic acid-induced learning and memory impairment.

Keywords: Ascorbic acid, dopamine D2 receptors, learning and memory, Morris water maze, rats

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Introduction

Vitamin C may be more than simply a "micronutrient" in the CNS, because it is present in millimolar concentrations in neuron-rich areas. A ascorbate has numerous functions in the CNS and brain. Although all actions of ascorbate involve the donation of a single electron, they can be divided into those considered antioxidant and non-antioxidant in nature. Recently, a neuromodulatory effect has been proposed for ascorbate (Fiona *et al*., 2009).

Several investigators have reported that ascorbic acid (AA) affects learning and memory processes. It has facilitatory effects on acquisition and retrieval processes in the rat passive avoidance learning and memory (Shahidi *et al*., 2008). In addition, ascorbic acid could reduce the risk of dementia caused by aging (Harrison *et al*., 2009a) and prevent learning and memory impairment due to the scopolamine (Harrison *et al*., 2009b). Recently, Tveden-Nyborg and colleagues (2009) reported that Vitamin C deficiency in early postnatal life impairs spatial memory.

There is a well-documented role for central dopamine systems in memory consolidation processes (El-Ghundi *et al*., 2007). Immediate post-training systemic administration of direct and indirect dopamine agonists can enhance retention in several tasks, including inhibitory avoidance, Y-maze visual discrimination and several versions of the radial-arm and Morris water mazes in rodents (Packard and White 1989; Castellano *et al*. 1991; Gasbarri *et al*., 1993; Packard and McGaugh 1994).

Furthermore, dopamine nonselective antagonist haloperidol can impaired later retention of a two-way avoidance task (Gozzani and Izquierdo 1976). Microinjection of the D2 antagonist sulpiride into either the nucleus accumbens or posteroventral caudate–putamen impaired different measures of retention in the hidden platform version of the Morris water maze (Setlow and McGaugh 1999a,b).

Systemic administration of the D2 antagonists has memory enhancing effects (Packard and McGaugh 1994; Setlow and McGaugh 1999a,b).

A complex interaction between ascorbate and dopaminergic system has been reported. Behavioral studies have demonstrated that ascorbate has an anti-dopaminergic property. High doses (1 g/kg) of ascorbate could block dopamine-mediated circling behavior, something that may also be achieved through dopamine receptor blockers (Tolbert *et al*., 1979). Although there is a clear complex relationship between ascorbate and the cholinergic and dopaminergic systems, available data suggest that ascorbate can behave as a dopamine receptor antagonist. In fact it has been shown that ascorbate inhibits the binding of specific D1 ([3H]SKF 38393) and D2 ([3H] N-0437) receptor agonists (Tolbert *et al*., 1992, Shimizu *et al*., 1989). In addition, ascorbate can be involved in the regulation of both acetylcholine and catecholamine release from synaptic vesicles (Kuo CH *et al*., 1979). Furthermore, D2 receptor antagonist sulpiride decreases striatal ascorbate release (Liu *et al*., 2000a).

However, the interaction between ascorbate and dopamine D2 receptor on special learning and memory has still not been elucidated and the present study was designed to examine such interaction.

Materials and methods

Animals

All experiments were carried out on male Wistar rats, weighing 200-250 g, that were housed one per cage under a 12 h light/dark cycle in a room with controlled temperature (22 ± $1^{°c}$). Food and water were available *ad libitum*. Animals were handled daily (between 9:00-11:00 AM) for 3 days before the experiment day in order to adapt them to manipulation and minimize nonspecific stress

responses. Rats were divided randomly into several experimental groups, each comprising 6-8 animals. All experiments were approved by the Animal Experimentation Ethic Committee of Shahid Bahonar University of Kerman. All tests were conducted between 9:00 and 13:00.

Drugs

Ascorbic acid (Sigma, USA) was dissolved in physiological saline. Sulpiride (Sigma, USA) was dissolved in a fresh 0.1 N HCl (pH 7.4). Bromocriptine (Sigma, USA) was dissolved in saline, propilenglycol and ethanol. The percentages of those solvents in the final volume were 50%, 40% and 10% respectively. All drugs were given in the volume of 10 µl (i.c.v.).

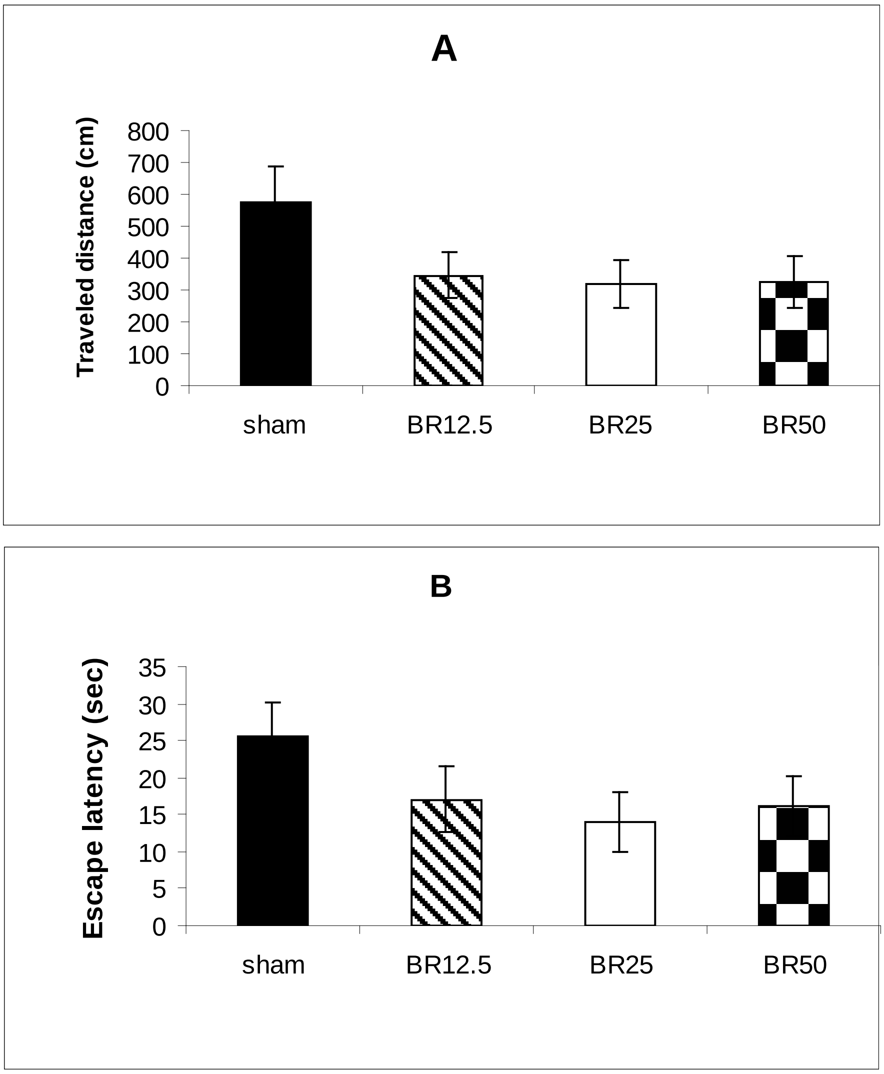


Figure 1. The effects of bromocriptiune during MWM training; Mean traveled distance (A) and escape latency (B) during 4 days of training in water maze with hidden platform. Error bars indicate ± S.E.M. n=7, BR= Bromocriptine

Behavioral procedure

The Morris task was assessed in a water tank (136 cm in diameter, 60 cm in height) filled with water (25±1 °C). The tank was located in a room containing several extra-maze visual cues fixed to the walls that were clearly visible from the pool. The escape platform testing was conducted in a 107-cm

diameter pool with a circular acrylic platform (10 cm diameter) submerged 2 cm below the surface of the water. The platform position was stable over 4 days . Rats were given four acquisition trials per day in a massed fashion and each rat completed all four trials before the next rat began its trials. A trail was terminated as soon as the rat had climbed onto the escape platform or when 90 s had elapsed. A rat was allowed to stay on the platform for 20 s and then the next trail was started. After completion of 4th trail, rats were gently dried and kept warm for an hour and then returned to their cages. On day 5 for the probe trial, the platform was removed and rats were released from the NE start point and were allowed to swim freely for 60s (Esmaeilpour and Abbasnejad., 2013). Animals were automatically tracked by a computerized system via an overhead TV camera. The path of each rat on each trail was analyzed by computing several parameters, e.g. latency to find the platform, traveled distance and percentage of traveled distance and time spent in the target quadrant.

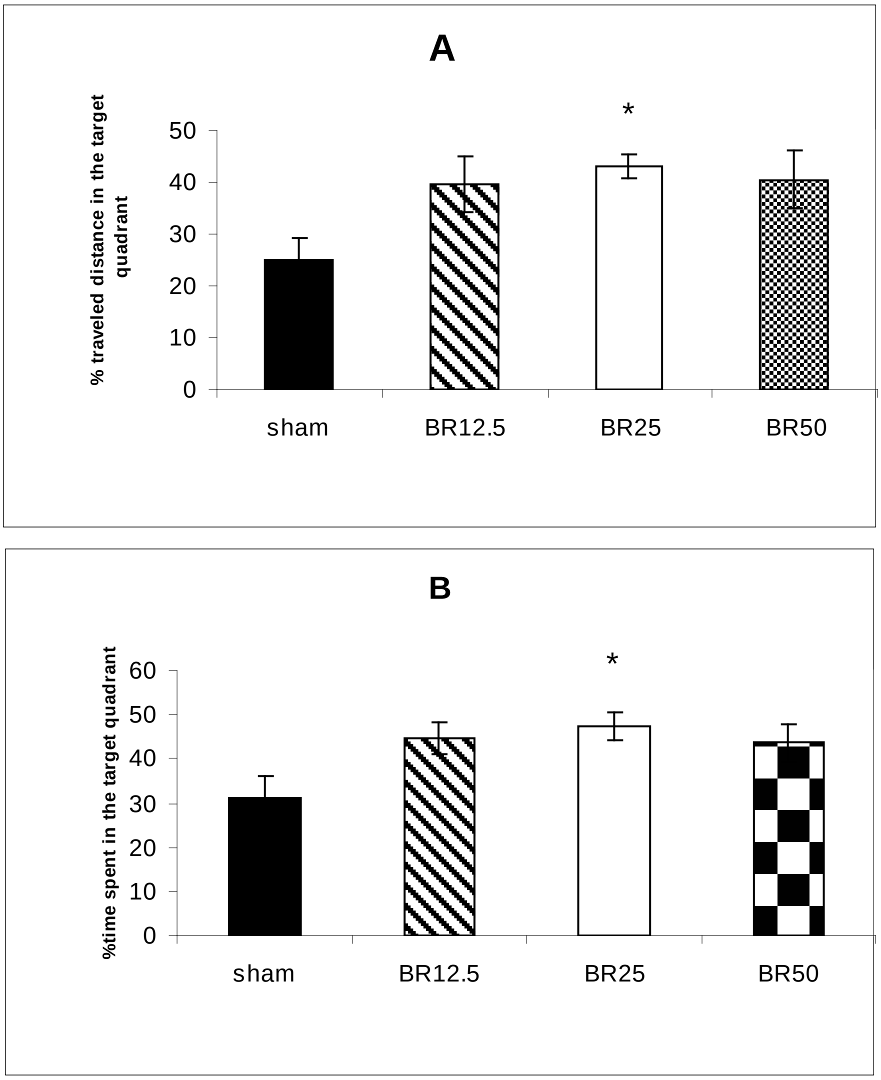


Figure 2. The effects of bromocriptine during MWM training; Percentage of traveled distances in target quadrant (A) and percentage of time spent in target quadrant (B) during the day 5 of training in water maze with the removal platform. Error bars indicate ± S.E.M. * *p*< 0.05 vs. sham. n=7, BR= Bromocriptine.

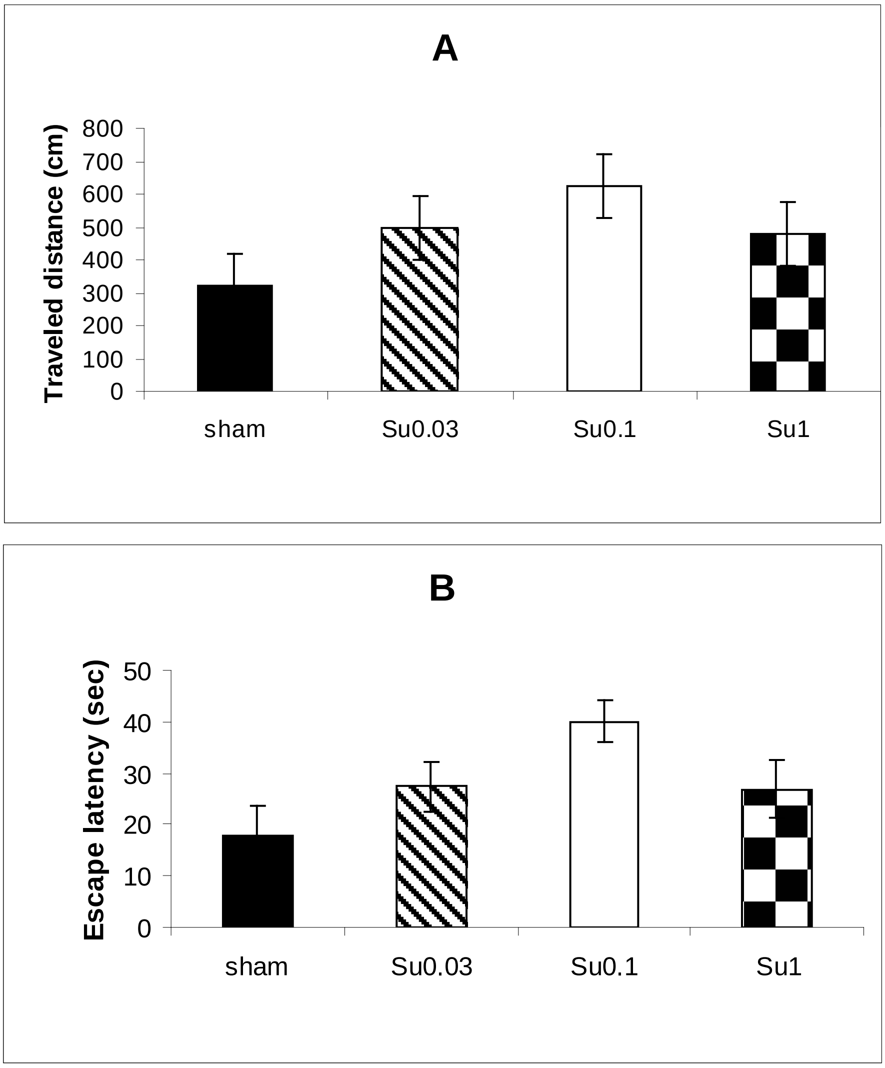


Figure 3. The effects of sulpiride during MWM training; Mean traveled distance(A) and escape latency (B) during 4 days of training in water maze with the hidden platform. Error bars indicate ± S.E.M. n=7, Su= Sulpiride

Experimental design

Animals were maintained in a special feeding cage for 3 days prior to the start of behavioral testing, so as to acclimate to procedures, including daily weighing, handling and the injection protocol. The rats were randomly assigned to the following groups. In ascorbate-treated group, ascorbate (25 µg, i.c.v.) was given. In sulpiride-treated group, sulpiride (0.03, 0.1 and 1 µg, i.c.v.) was administrated in 09.00 a.m. Ascorbate and sulpiride were given concomitantly in third group. In bromocriptine-treated group, bromocriptine (12.5, 25 and 50 µg, i.c.v.) was given. Ascorbate and bromocriptine were given concomitantly in another group. Saline and vehicles were injected as sham control group.

Statistical analysis

The results are expressed as mean ± SEM. The data of first four training days with hidden platform were subjected to a two-way analysis of variance (ANOVA) followed by the Tukey test. Data of the 5th day with visible platform were analyzed by one-way ANOVA. $P < 0.05$ was considered significant.

Results

1. The effect of Bromocriptine

1.1. Hidden platform trials(days 1-4)

Figs 1 shows the results obtained from the injection of different doses of bromocriptine (12.5, 25 and 50 µg/rat) and its vehicle. There were no significant differences between groups in traveled distances (fig. 1A) and escape latency (fig. 1B).

1.2. Remove platform trials (day 5)

There were significant differences (p<0.05) in the percentage of traveled distances in the target quadrant of Br (25 µg/rat) and vehicle treated animals on the day 5 (Fig. 2A). The percentage of time spent in the target quadrant was statistically significant between Br(25 µg/rat: p <0.05) and sham on the day 5 (Fig. 2B).

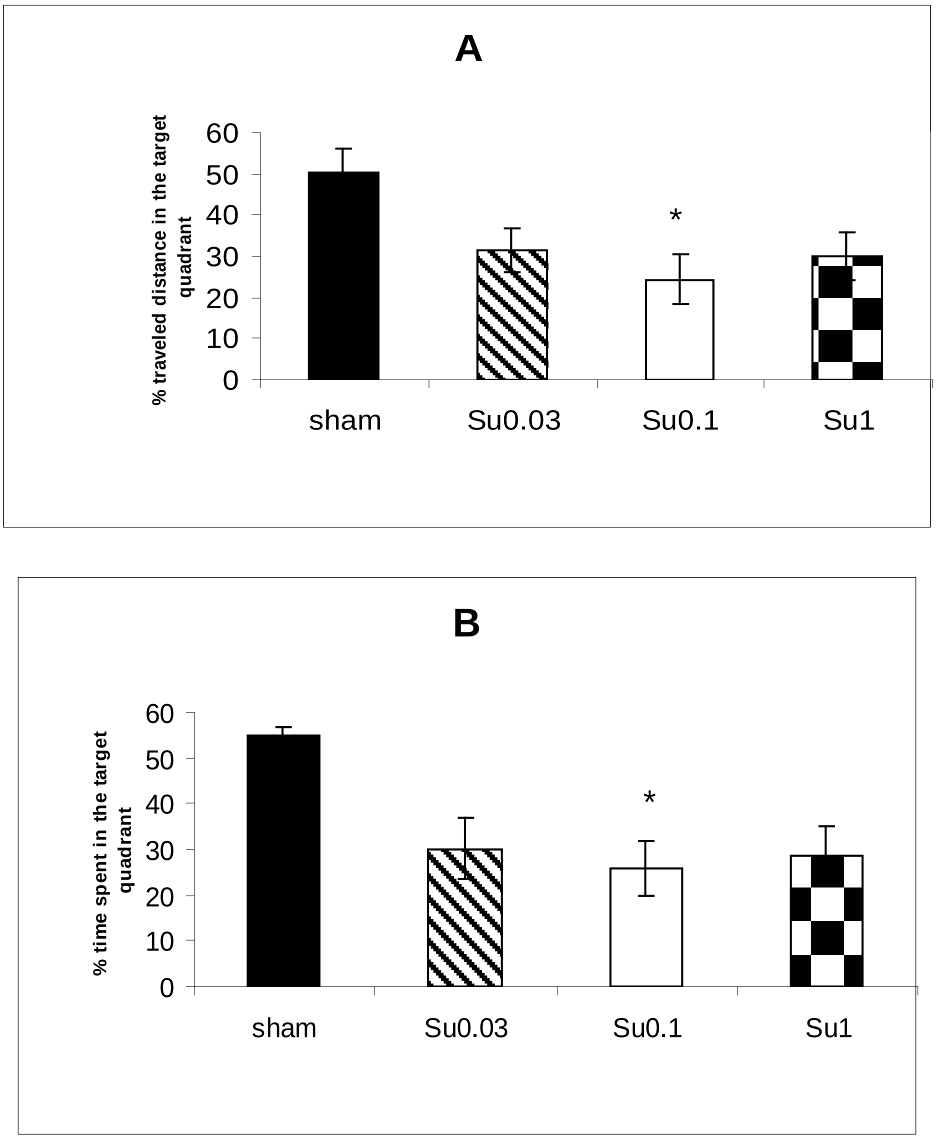


Figure 4. The effects of sulpiride during MWM training; Percentage of traveled distances in the target quadrant (A) and Percentage of time spent in target quadrant (B) during the day 5 of training in water maze with the removal platform. Error bars indicate ± S.E.M. * *p*< 0.05 vs. sham. n=7, Su= Sulpiride

2. The effect of Sulpiride

2.1. Hidden platform trials (Days 1-4)

Figs 3 A and B show the results obtained from the injection of different doses of sulpiride (0.03, 0.1 and 1 µg/rat) and its vehicle. There were no significant differences between groups in traveled distances (fig. 3A) and escape latency parameters (fig. 3B).

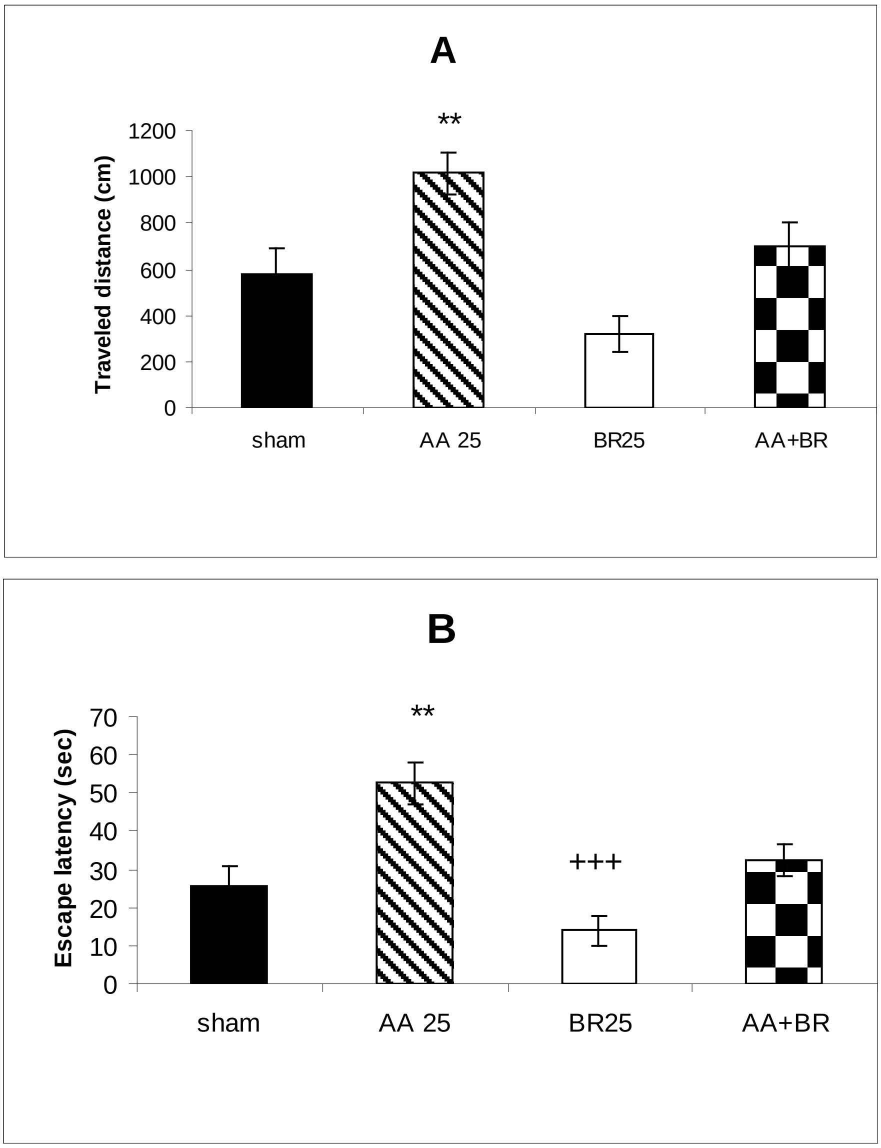


Figure 5. The effects of Co- administration of Ascorbic acid plus bromocriptine during MWM training; Mean traveled distance(A) and escape latency (B) during 4 days of training in water maze with hidden platform. Error bars indicate ± S.E.M. ** *p* < 0.01 vs. Br. 25(in fig. A) , ** *p* < 0.01 vs. sham, +++ *p* <0.001 vs AA.25 (in fig. B) , n=7, AA= Ascorbic acid, BR= Bromocriptine

2.2. Remove platform trials (day 5)

There was significant difference of performance among sulpiride (0.1 µg/rat) and vehicle treated animals on the day 5 in percentage of traveled distances values in the target quadrant (*p* <0.05) (Fig. 4A). Percentage of time spent in the target quadrant was not significantly different in performance between

groups(Fig. 4B).

3. The effect of co-administration of ascorbic acid and bromocriptine

3.1. Hidden platform trials (Days 1-4)

Figs. 5 A and B show the results obtained from the injection of Ascorbic acid(25 μg/rat) plus bromocriptine(25 μg/rat) and group receiving vehicle (Propylenglycol+ saline) as sham. A significant difference was found in traveled distances between(AA 25 μg/rat: p <0.01) and Br (Fig. 5A). A significant difference was found in escape latency between(AA 25 μg/rat: p <0.01) and sham and between (Br 25 μg/rat) and (AA 25 μg/rat: p <0.001) (Fig. 5B).

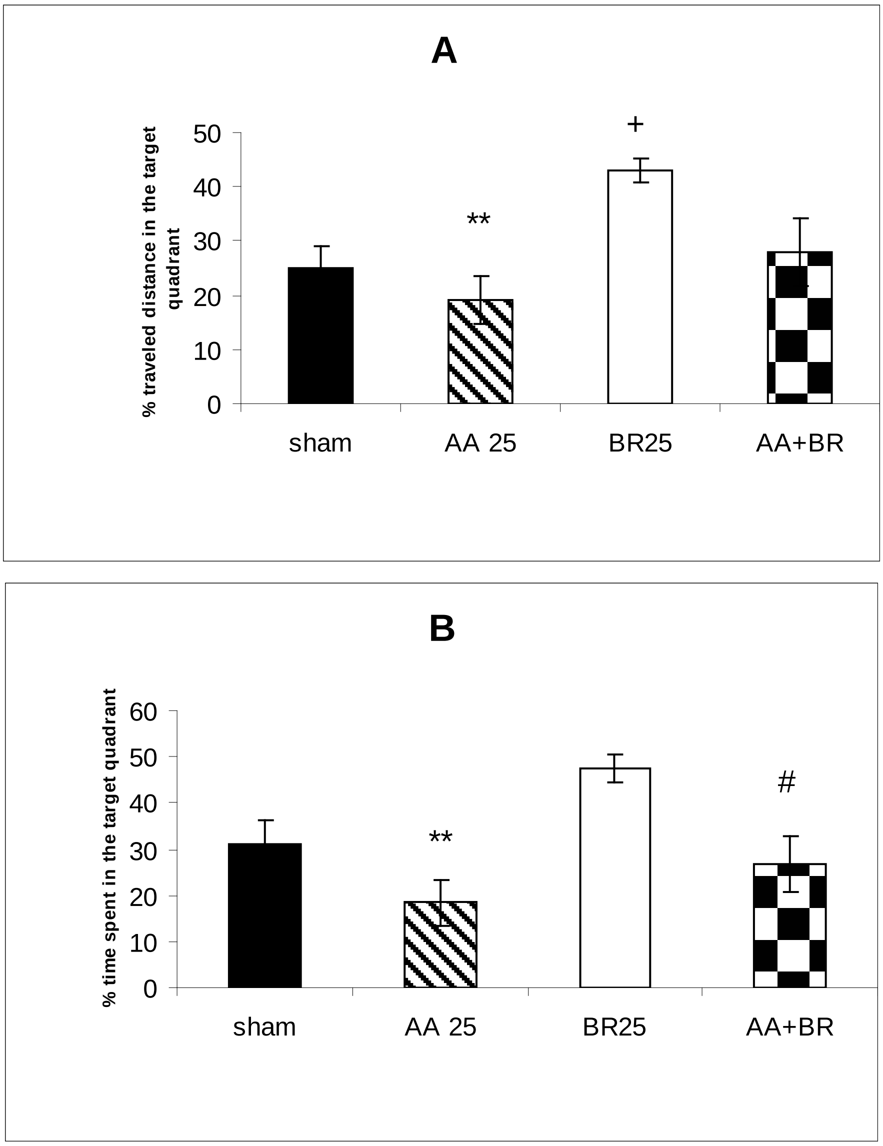


Figure 6. The effects of Co- administration of Ascorbic acid plus bromocriptine during MWM training; Percentage of traveled distances in target quadrant (A) and Percentage of time spent in the target quadrant (B) during the day 5 of training in water maze with the removal platform. Error bars indicate ± S.E.M. ** *p* <0.05 vs. Br. 25, + *p* < 0.05 vs. sham (fig. A), # *p* <0.05 vs. Br. 25, ** *p* < 0.01 vs. Br.25(fig. B), n=7, AA= Ascorbic acid, BR= Bromocriptine.

3.2. Remove platform trials(day 5)

A significant difference was observed in the percentage of traveled distances in the target quadrant between animals that had AA (25 µg/rat) and Br (25 µg/rat, p <0.01) and also between Br (25 µg/rat, p <0.05) and vehicle-treated groups (Fig. 6A). Furthermore, a significant difference was found in the percentage of time spent in the target quadrant between AA- and Br-injected animals (p < 0.01) as well as between animals that received AA+Br and Br only (p < 0.05) (Fig. 6B).

4. The effect of co-administration of ascorbic acid and sulpiride

4.1. Hidden platform trials(days 1-4)

Figs. 7 A and B show the effect of ascorbic acid (25 µg/rat) plus sulpiride (0.1 µg/rat) on learning and memory indices. A significant difference was observed in the traveled distances between AA (25 µg/rat) alone and sham groups (p <0.01) and also between animals that had Su (0.1 µg/rat) and AA (25 µg/rat) alone (p <0.05) (Fig. 7A). A significant difference was also found in time spent between AA and sham control groups (p <0.05) and also between Su+AA and sham groups (Fig. 7B).

4.2. Remove platform trials(day 5)

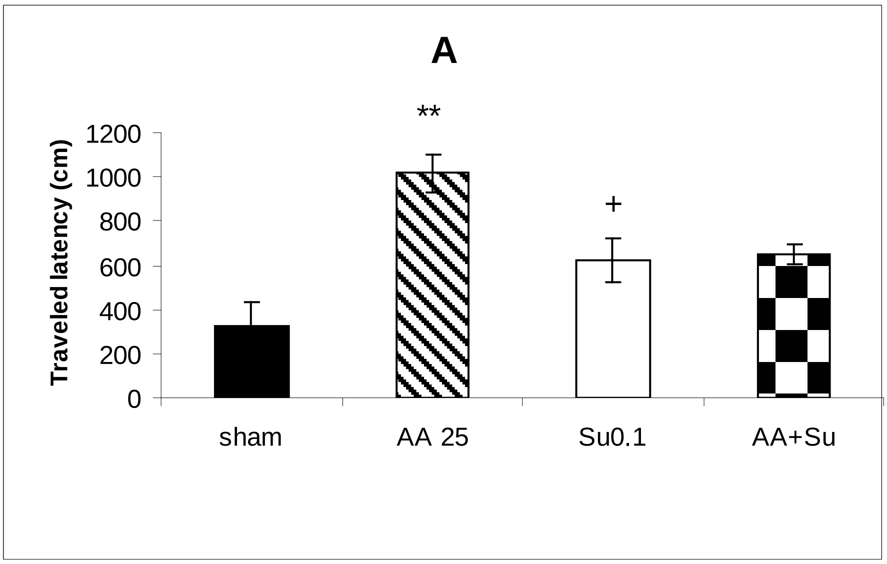
Percentage of traveled distances in the target quadrant was significantly different between (AA 25 µg/rat: p <0.01), (Su 0.1 µg/rat: p <0.01), (Su 0.1 µg/rat+ AA 25 µg/rat: p <0.01) and sham (Fig. 8A) and in the percentage of time spent in the target quadrant between (AA 25 µg/rat: p <0.01), (Su 0.1 µg/rat: p <0.05), (Su 0.1 µg/rat+ AA 25 µg/rat: p <0.01) and sham (Fig. 8B).

Discussion

There is no study regarding the effect of ICV injection of AA on cognitive indices in rats. AA is considered not only as an antioxidant but also as a neuromodulator (Dai *et al*., 2006). Our present experiments showed that central injection of bromocriptine as a D2 selective agonist increases spatial memory, while co-administration of ascorbic acid and bromocriptine decreased spatial memory. Therefore, it seems that ascorbic acid attenuates the learning promoting effect of bromocriptine. Injection of D2 selective antagonist sulpiride alone or in combination with ascorbic acid decreased spatial memory. It is documented that AA can interfere with glutamatergic, dopaminergic, cholinergic and GABAergic transmission and their related behavior (Fiona *et al*., 2009). These neurotransmitter systems have a basic and critical role in learning and memory processes (Myhrer *et al*., 2003). It has been demonstrated that method of administration, (Shahidi *et al*., 2008) animal age and period of injection (Arzi *et al*., 2004) have an influencing and important role in the effect of AA on learning and memory. In addition, numerous studies have shown that the anti-impairment effects of AA on learning and memory are due, at least in part, to its antioxidant effects (Castagne *et al*., 2004, Cho *et al*., 2003, Reis *et al*., 2002). This issue is in a contradiction with our results that show central injection of AA has a decreasing effect on learning and memory indices in MWM task. In our previous study, central administration of ascorbic acid significantly decreased learning and spatial memory (abbasnejad *et al*., 2008). This study is in agreement with previous findings (Luciana 1997, D'Esposito 2008, Ichihara 1989) showing that ICV injection of Br can increase but Su decrease learning and memory indices.

It has been reported that acute systemic injection of ascorbic acid has no significant effect on passive avoidance learning (PAL) and memory in rats. In addition, short- and long term ascorbic acid treatment decrease learning acquisition (Shahidi *et al*., 2008). AA could potentiate amphetamine-induced dopamine release in both the nucleus

accumbens and neostriatum (Pierce *et al,*. 1995).



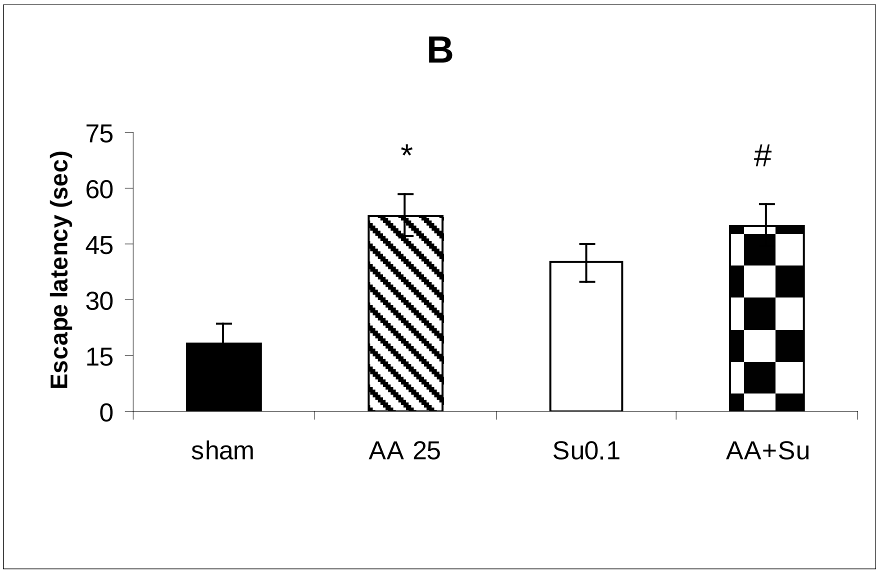


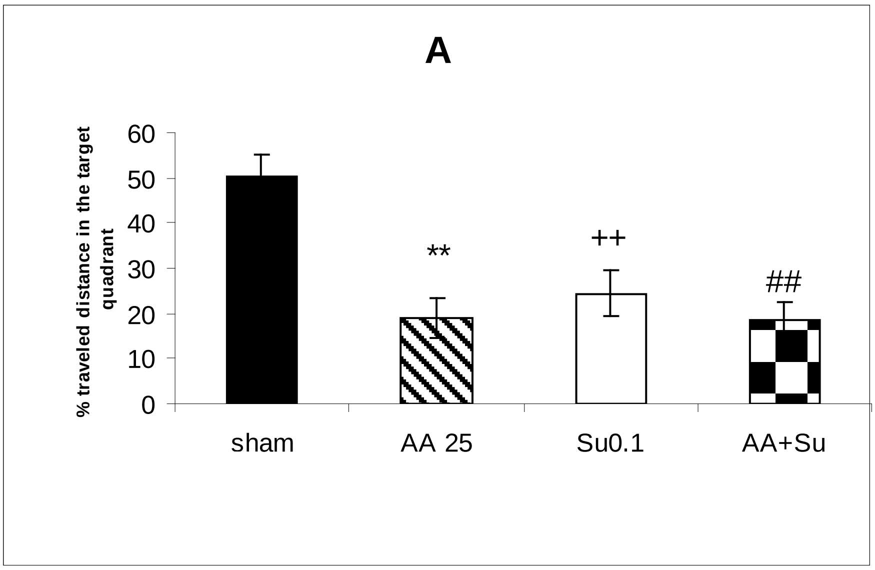
Figure 7. The effects of Co- administration of Ascorbic acid plus sulpiride during MWM training; Mean traveled distance(a) and escape latency (b) during 4 days of training in water maze with hidden platform. Error bars indicate ± S.E.M. *****p*< 0.01 vs. sham, +** ***p*** **<0.05 vs. AA.25, *** ***p*** **< 0.05 vs. sham, #** ***p*** **<0.0015 vs sham , n=7, AA= Ascorbic acid, Su= Sulpiride**

It has been demonstrated that ascorbate releasing is regulated, at least in part, by dopaminergic mechanisms, which appear to be involved through both the D1 and D2 family of dopamine receptors (Rebec *et al*., 1994). In both normal and 6-hydroxydopamine-treated rats sulpiride has a decreasing effect on basal and ethanol-induced ascorbic acid release (Liu *et al*., 2000a). Furthermore, AA can modulates dopamine and glutamate in mammalian telencephalon (Majewska *et al*., 1990, Rebecca *et al*., 1994) and dopamine regulates brain extracellular AA levels (Phebus *et al*., 1990).

AA releasing from glutamatergic neurons is a D1 and D2 receptor mediated mechanism. Dopamine agonists facilitate the release of AA from glutamatergic terminals and dopamine

antagonists can inhibit this phenomenon (Rebec *et al*., 1994). It has been reported that ascorbate facilitates spatial learning when is used in low or average doses and conversely impairs it when used in high doses (Esmaili *et al*., 2003). Ascorbic acid with low and high concentration has agonistic and antagonistic effects on both dopaminergic and glutamatergic systems, respectively. It seems that these two systems directly affect learning and memory.

The above mentioned documents suggest that dopamine D2 receptors might be involved in central AA-induced learning and memory impairment. However, further investigation is necessary to evaluate the exact mechanism(s) of learning and memory decreasing effect of AA in lateral ventricles. Taken together, this study shows that the ICV injection of AA attenuated the positive effects of D2 dopamine receptors agonist on spatial memory and learning.



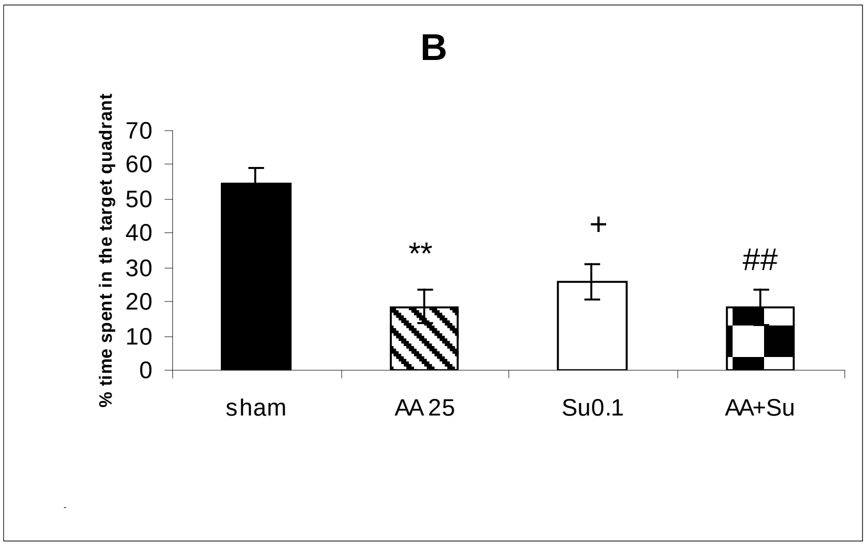


Figure 8. The effects of Co- administration of Ascorbic acid plus sulpiride during MWM training; Percentage of traveled distances in target quadrant (A) and Percentage of time spent in target quadrant (B) during the day 5 of training in water maze with the removal platform. Error bars indicate ± S.E.M. ** *p* <0.01 vs. sham, ++ *p* <0.01 vs. sham, ## *p* <0.01 vs. sham, + *p* < 0.05 vs. sham, n=7, AA= Ascorbic acid, Su= Sulpiride.

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References

Abbasnejad, M., Nasri, S., Nazem, H., Bahaaddini, M. (2008) The effect of ascorbic acid injection into the lateral ventricle on spatial learning and memory in adult male rats. *Physiology and Pharmacology* **12**, 227-237.

Arzi, A., Hemmati, A.A., Razian, A. (2004) Effect of Vitamins C and E on cognitive function in mouse. *Pharmacol* **49**, 249-252.

Castagne, V., Rougemont, M., Cuenod, M., Do, K.Q. (2004) Low brain glutathione and ascorbic acid associated with dopamine uptake inhibition during rat's development induce long-term cognitive deficits: relevance to schizophrenia. *Neurobiology* **15**, 93-105.

Castellano, C., Cestari, V., Cabib, S., Puglisi-Allegra, S. (1991) Post-training dopamine receptor agonists and antagonists affect memory storage in mice irrespective of their selectivity for D1 or D2 receptors. *Behavioral and Neural Biology* **56**, 283–291.

Cho, J., Kang, J.S., Long, P.H., Jing, J., Back, Y., Chung, K.S. (2003) Antioxidant and memory enhancing effects of purple sweet potato anthocyanin and cordyceps mushroom extract. Arch *Pharmacol* **26**, 821-825.

Dai, F., Yang, J. Y., Gu, P. F., Hou, Y., Wu, Ch. F. (2006) Effect of drug-induced ascorbic acid release in the striatum and the nucleus accumbens in hippocampus-lesioned rats. *Brain Research* **1125**(1), 163–170.

D'Esposito, M. (2008) Working memory. *Neuropsychology and behavioral neurology* **88**, 241-247.

El-Ghundi, M., O'Dowd, B.F., George, S.R. (2007) Insights into the role of dopamine receptor systems in learning and memory. *Reviews in the neurosciences* **18**(1), 37-66.

Esmail, M.H., Doodangeh, E., Sharif,i M. (2003) The effect of ascorbic acid on spatial learning. *The Journal of Qasvin* **24**, 3-8

Esmaeilpour-Bezenjani., Kh. and Abbasnejad., M. (2013) Effect of administration of ascorbic acid and dopamine D2 receptors agonist in the hippocampal CA1 area on spatial learning and memory in adult male rats. *Iranian Journal of Veterinary Research*, **14**(2), 126-132.

Fiona, E., Harrison, James, M. (2009) May Vitamin C function in the brain: vital role of the ascorbate transporter SVCT2. *Free Radical Biology and Medicine* **46**(6), 719-730.

Gasbarri, A., Introini-Collison, I.B., Packard, M.G., Pacitti, C., McGaugh, J.L. (1993) Interaction of cholinergic-dopaminergic systems in the regulation of memory storage in aversively motivated learning tasks. *Brain Research* **627**, 72–78.

Gozzani, J.L., Izquierdo, I. (1976) Possible peripheral adrenergic and central dopaminergic influences in memory consolidation. *Psychopharmacology* **49**, 109–111.

Harrison, F.E., Hosseini, A.H., Dawes, S.M., Weaver, S., May, J.M. (2009) Ascorbic acid attenuates scopolamine-induced spatial learning deficits in the water maze. *Behavioral Brain Research* **205**, 550–558.

Harrison, F.E., Hosseini, A.H., McDonald, M.P., Dawes, S.M., Weaver, S., May, J.M. (2009) Vitamin C reduces spatial learning deficits in middle-aged and very old APP/PSEN1 transgenic and wild-type mice. Pharmacology. *Biochemistry and Behavior* **93**, 443–

450.

Harrison, F.E. and May, J.M. (2009) Vitamin C function in the brain, vital role of the escaped transporter SVCT. *Free Radical Biology and Medicine* **15**, 719-730.

Ichihara, K. (1989) Differential effects of pimoside and SCH23390 on acquisition of learning in mice. *European Journal of Pharmacology* **164**, 189-195.

Kuo, C.H., Hata, F., Yoshida, H., Yamatodani, A., Wada, H. (1979) Effect of ascorbic acid on the release of acetylcholine from synaptic vesicles prepared from different species of animals and release of noradrenaline from synaptic vesicles of rat brain. *Life Science Journal* **24**(10), 911-915.

Landmark, K. (2006) Could intake of vitamins C and E inhibit development of Alzheimer dementia? Tidsskr. No. *Laegeforen* **126**, 159–161.

Liu, W., Wu, C.F., Hung, M., Xiao, K. (2000) Opposite effects of sulpiride and SCH23390 on ethanol-induced striatal ascorbic acid release in intact and 6-hydroxy dopamine lesioned rats. *Brain Research* **869**, 31-38.

Luciana, M. and Collins, F. (1997) Dopaminergic modulation of working memory for spatial but not object cues in normal humans. *Cognitive Neuroscience* 9, 330-347.

Majewska, M.B., Bell, J.A., London, E.D. (1990) Regulation of the NMDA receptor by redox phenomena-Inhibitory role of ascorbate. *Brain Research* **537**, 328-332.

Myhrer, T. (2003) Neurotransmitter systems involved in learning and memory in the rat: a meta-analysis base on studies of four behavioral tasks. *Brain Research* **41**, 268-287.

Packard, M.G. and McGaugh, J.L. (1994) Quinpirole and d-amphetamine administration posttraining enhances memory for spatial and cued discriminations in a water maze. *Psychobiology* **22**, 54–60.

Packard, M.G. and White, N.M. (1989) Memory facilitation produced by dopamine agonists: Role of receptor subtype and mnemonic requirements. Pharmacology, *Biochemistry and Behavior* **33**, 511–518.

Pal, M. and Dhingra, D. (2003) Ascorbic acid: a promising memory-enhanced in mice, *Journal of Pharmacological Sciences* **93**, 129–135.

Phebus, L.A., Roush, M.E., Clemens, J.A., (1990) Effect of direct and indirect dopamine agonists on brain extracellular ascorbate levels in the striatum and nucleus accumbens of awake rats. *Life Sciences* **47**, 1317-1323.

Pierce, R.C., Rowlett, J.K., Rebec, G.V., Bardo, M.T. (1995) Ascorbate potentates amphetamine-induced conditioned place preference and forebraindopamine release in rats. *Brain Research* **688**, 21–26.

Rebec, G.V. and pierce, C.P. (1994) A Vitamin as neuromodulator: ascorbate release into the extracellular fluid of the brain regulates dopaminergic and glutaminergic transmission. *Progress in Neurobiology* **43,** 537-565.

Reis, E.A., Zugno, A.I., Franzon, R., Tagliari, B., Matte, C., Lammers, M.L. (2002) Pretreatment with vitamins E and C prevent the impairment of memory caused by homocysteine administration in rats. *Metabolic Brain Disease* **17**(3), 211-217.

Setlow, B. and McGaugh, J. (1999) Differential effects of immediate post-training sulpiride infusions into the nucleus accumbens core and shell on retention in the Morris water maze. *Psychobiology* **27**, 248–255.

Setlow, B. and McGaugh, J. (1999)

Involvement of the posteroventral caudate-putamen in memory consolidation in the Morris water maze. *Neurobiology of Learning and Memory* **71**, 240–247.

Shahidi, S., Komaki, A., Mahmoodi, M., Atrvash, N., Ghodrati, M. (2008) Ascorbic acid supplementation could affect passive avoidance learning and memory in rats. *Brain Research Bulletin* **76**, 109-1113.

Shimizu, H., Bray, G.A. (1989) Hypothalamic monoamines measured by microdialysis in rats treated with 2-Deoxy–Glucose or fenfluramine. *Physiology* & *Behavior* **46**, 799-807.

Tolbert, L.C., Thomas, T.N., Middaugh, L.D., Zemp, J.W. (1979) Ascorbate blocks amphetamine-induced turning behavior in rats with unilateral Nigro-striatal lesions. *Brain Research Bulletin* **4**(1), 43-48.

Tolbert, L.C., Morris, P.E., J.r., Spollen, J.J., Ashe, S.C. (1992) Stereospecific effects of ascorbic acid and analogues on D1 and D2 agonist binding. . *Life Sciences* **51**(12), 921-930.

Tveden-Nyborg, P., Johansen, L.K., Raida, Z., Villumsen, C.K., Larsen. J.O., Lykkesfeldt, J. (2009) Vitamin C deficiency in early postnatal life impairs spatial memory and reduces the number of hippocampal neurons in guinea pigs. *American Journal* of *Clinical Nutrition* **90**, 540-546.

بررسی تداخل مرکزی اسیداسکوربیک با آگونیست و آنتا گونیست گیرندههای دوپامینی D2 بر یادگیری و حافظه فضایی موشهای صحرایی نر بالغ

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چکیده

مطالعات قبلی نشان داده اند که سطح خارج سلولی اسیداسکوربیک بر گیرندههای دوپامینی تأثیرتعدیلی دارد. گیرندههای اسیداسکوربیک و دوپامین هر دو نقش مهمی در فرایندهای یادگیری و حافظه دارند، به هر حال تعامل مرکزی اسیداسکوربیک و گیرنده D2 دوپامینی بر یادیگری و حافظه هنوز توضیح داده نشده است.

تمامی آزمایشها، بر روی موشهای صحرایی نر نژاد wistar صورت پذیرفت. حیوانات به مدت ۵ روز در ماز آبی موریس، ۴ روز با وجود سکوی غیرقابل مشاهده مخصوص تست یادگیری و روز پنجم بدون سکوی قابل دید برای تست انگیزه و هماهنگی حسی و حرکتی مورد آموزش قرار میگرفتند.

دادهها نشان میدهد که اسیدآسکوربیک (25µg i.c.v) یادگیری و حافظه فضایی مورد ارزیابی به وسیله تست ماز آبی موریس را بهبود میبخشد. تزریق بروموکریپتین آگونیست گیرنده D2 موجب افزایش تأثیر اسیدآسکوربیک و درمان بهوسیله آنتاگونیست انتخابی گیرنده D2 سولپیراید منجر به کاهش حافظه ناشی از اثر اسکوربات میگردد. این نتایج نقش گیرندههای دوپامینی را در تأثیرات اسیداسکوربیک بر یادگیری و حافظه نشان میدهند.

واژگان کلیدی: اسیداسکوربیک، گیرندههای D2 دوپامینی، یادگیری و حافظه، ماز آبی موریس، موشهای صحرایی